REMARKS

This responds to the Office Action mailed on June 1, 2009.

Claims 1, 3-4, 9-11, 17, 21-22, 27, 35, 39, and 46 are amended, claims 2, 19-20 and 25-26 are canceled, and claim 48 is added; as a result, claims 1, 3-18, 21-23, 27-46, and 48 are pending.

The 35 U.S.C. § 112 Rejection

Claims 1, 4-11, 17-19, 25, 30-31, 35-37, and 41-44 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. This rejection is respectfully traversed.

The Examiner asserts that the metes and bounds of "enhanced protein degradation" in claim 1 is not clear.

Claim 1 recites that the presence of the at least two different protein destabilization sequences in the fusion polypeptide results in enhanced protein degradation relative to a fusion polypeptide with one of the protein destabilization sequences. Therefore, one of skill in the art would understand the metes and bounds of "enhanced protein degradation" in the context of the claims.

Therefore, withdrawal of the 35 U.S.C. § 112, second paragraph, rejection is respectfully requested.

The 35 U.S.C. § 103 Rejection

Claims 1-11, 15-20, 25, 30-32, 34-37, and 41-44 were rejected under 35 U.S.C. § 103(a) as being obvious over Daly (U.S. Patent No. 7,157,272) and Gilon et al. (EMBO J., 17:2759 (1998)). This rejection is respectfully traversed.

The application which issued as the Daly patent (Serial No. 10/658,093) was filed on September 9, 2003 and is a continuation in part of PCT/AU02/00351, filed on March 8, 2002, which relies on the filing date of U.S. application Serial No. 60/274,770, filed on March 9, 2001. The present application claims the benefit of the filing date of September 16, 2002. Although Applicant presents arguments below in support of the patentability of the pending claims,

Applicant reserves the right to swear behind one or more of the respective filing dates of the Daly applications mentioned above.

Claim 1

Applicant respectfully traverses the rejection and submits that the Office Action does not set forth a proper *prima facie* case of obviousness because the cited portions of Daly and Gilon et al., individually or in combination with each other, and reasoning given in the Office Action, do not provide the claimed subject matter. For example, Applicant is unable to find in the cited portions of Daly and Gilon et al., individually or in combination, among other things, an isolated nucleic acid molecule comprising a nucleic acid sequence encoding a fusion polypeptide comprising a reporter protein and at least two different heterologous protein destabilization sequences both of which are C-terminal to the reporter protein, wherein one heterologous protein destabilization sequence is SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, or SEQ ID NO:98, wherein another heterologous protein destabilization sequence includes a sequence enriched in proline, glutamic acid, serine, and/or threonine residues (a PEST sequence), wherein the reporter protein is luciferase, fluorescent protein, chloramphenicol acetyltransferase, beta-glucuronidase or beta-galactosidase, and wherein the presence of the at least two different protein destabilization sequences in the fusion polypeptide in a mammalian cell results in enhanced protein degradation relative to a fusion polypeptide with one of the protein destabilization sequences in a corresponding mammalian cell, as recited in claim 1. Applicant is unable to find in the Office Action a proper reason that remedies this deficiency.

The Examiner asserts that one of skill in the art would have been motivated to add the protein destabilizing sequence of Gilon et al. or to substitute the N-terminal degradation signal of Daly with the C-terminal degradation signal of Daly. to further reduce the half-life of luciferase in the fusion protein of Daly. However, if the half-life of a fusion polypeptide with only one protein destabilizing sequence is "about 20-30 minutes" (page 6 of the Office Action), it is unclear why one of skill in the art would prepare a reporter protein with even a shorter half-life. The Examiner has failed to provide a rationale for preparing such a reporter protein.

Additionally, Applicant is unable to find in the Office Action a reason why one of ordinary skill in the art would have had reasonable expectation of success in the combination of the cited references. That is because, based on the results in Corish et al. (Protein Eng., 12:1035 (1999)) (of record), one of skill in the art was apprised that a reporter protein linked to a combination of two different protein destabilization sequences (a murine ODC that contains a PEST sequence and a murine cyclin B1 fragment that contains a destruction box (CDB)) did not have a substantially reduced half-life relative to a reporter protein linked to the "dominant" protein destabilization sequence of the two (i.e., no additive or complementing effect). Recall that Corish et al. disclose that "[t]he addition of the PEST motif to this CDB-GFP protein **marginally** reduced the average half-life further to 5.5 hours…Thus, addition of the PEST region does not appear to make a **significant** difference to fluorescence when protein levels are non-limiting" (emphasis added; page 1037).

Moreover, consider that Corish et al. expressed fusion proteins having murine protein destabilization sequences in mouse cells (LA-9 cells) and Daly expressed fusion proteins with murine derived protein destabilization sequences in human cells (HeLa cells), i.e., both the protein destabilization sequence and host cell were mammalian in origin. Because the protein destabilization sequences in Gilon et al. were yeast protein destabilization sequences and fusion proteins having those protein destabilization sequences linked to a reporter protein or a selectable protein in Gilon et al. were expressed in yeast, one of skill in the art would not have a reasonable expectation that yeast protein destabilization sequences would be useful in heterologous cells, such as mammalian cells, much less have an additive or complementing effect with other protein destabilization sequences.

Further, prior to Applicant's disclosure it was unknown whether different protein destabilization sequences at the C-terminus of a protein could have complementing effects. And in view of Corish et al., it was unexpected that different protein destabilization sequences could have complementing effects. As shown in Figure 8 in the specification, there was a more rapid decrease over time in luminescence in CHO cells expressing luciferase-CL1-PEST (luminescent half-life of less than about 20 minutes) relative to CHO cells expressing luciferase-PEST (luminescent half-life of about 60 minutes) or CHO cells expressing luciferase-CL (luminescent half-life of about 120 minutes) after cycloheximide treatment (luciferase-CL1-PEST <

luciferase-PEST < luciferase-CL1). It was also unexpected that there was a more rapid and/or significant increase in luminescence after induction of luciferase-CL1-PEST relative to luciferase-PEST (see Figures 10B and 12). Thus, the properties of a fusion protein with different protein destabilization sequences, one of which is a yeast protein destabilization sequence, were unexpected.

Applicant respectfully requests reconsideration and allowance of claim 1.

Claims 2-11, 15-20, 25, 30-32, 34-37, and 44

Applicant respectfully traverses the rejection.

Claims 2, 19-20 and 25 are canceled.

Claims 3-11, 15-18, 30-32, 34-37, and 44 are dependent on claim 1, which is believed to be allowable for at least the reasons set forth above. Therefore, the discussion above for claim 1 is incorporated herein to support the patentability of claims 3-11, 15-18, 30-32, 34-37 and 44.

Applicant respectfully requests reconsideration and allowance of claims 3-11, 15-18, 30-32, 34-37, and 44.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 30th day of September, 2009.

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